Fibrosis and wall thickness affect ventricular repolarization dynamics in hypertrophic cardiomyopathy

Jalanko, Mikko

2018-11

Jalanko , M , Väänänen , H , Tarkiainen , M , Sipola , P , Jääskeläinen , P , Lauerma , K , Laitinen , T , Laitinen , T , Laine , M , Heliö , T , Kuusisto , J & Viitasalo , M 2018 , ' Fibrosis and wall thickness affect ventricular repolarization dynamics in hypertrophic cardiomyopathy ' , Annals of Noninvasive Electrocardiology , vol. 23 , no. 6 , 12582 . https://doi.org/10.1111/anec.12582

http://hdl.handle.net/10138/307722
https://doi.org/10.1111/anec.12582

publishedVersion

Received: 29 November 2017 | Revised: 11 May 2018 | Accepted: 6 June 2018

DOI: 10.1111/anec.12582

ORIGINAL ARTICLE

WILEY

Fibrosis and wall thickness affect ventricular repolarization dynamics in hypertrophic cardiomyopathy

Mikko Jalanko[1] | Heikki Väänänen[2] | Mika Tarkiainen[3] | Petri Sipola[3] | Pertti Jääskeläinen[3] | Kirsi Lauerma[4] | Tiina Laitinen[5] | Tomi Laitinen[5] | Mika Laine[1] | Tiina Heliö[1] | Johanna Kuusisto[6] | Matti Viitasalo[1]

[1]Department of Cardiology, Heart and Lung Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[2]Department of Neuroscience and Biomedical Engineering, Aalto University, Espoo, Finland

[3]Department of Radiology, Kuopio University Hospital, Kuopio, Finland

[4]Department of Radiology, Helsinki University Hospital, Helsinki, Finland

[5]Department of Clinical Physiology, Kuopio University Hospital, Kuopio, Finland

[6]Centre for Medicine and Clinical Research, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland

Correspondence
Mikko Jalanko, Helsinki University Hospital, Heart and Lung Center, Department of Cardiology, Haartmaninkatu 4, PB 340, FIN-00029 HUS, Finland.
Email: mikko.jalanko@hus.fi

Funding information
Finnish Foundation of Cardiovascular Research, the special governmental subsidy for health sciences research of the University Hospital of Kuopio, Finnish Medical Foundation, the Ida Montin Foundation, and the Finnish Academy.

Abstract

Background: Hypertrophic cardiomyopathy (HCM) is characterized by ventricular repolarization abnormalities and risk of ventricular arrhythmias. Our aim was to study the association between the phenotype and ventricular repolarization dynamics in HCM patients.

Methods: HCM patients with either the *MYBPC3*-Q1061X or *TPM1*-D175N mutation (n = 46) and control subjects without mutation and hypertrophy (n = 35) were studied with 24-hr ambulatory ECG recordings by measuring time intervals of rate-adapted QT (QTe), maximal QT, and T-wave apex to wave end (TPE) intervals and the QTe/RR slope. Findings were correlated to specified echocardiographic and cardiac magnetic resonance imaging (CMRI) findings.

Results: Rate-adapted QTe interval was progressively longer in HCM patients with decreasing heart rates compared to control subjects (p = 0.020). The degree of hypertrophy correlated with measured QTe values. HCM patients with maximal wall thickness higher than the mean (20.6 mm) had longer maximum QTe and median TPE intervals compared to control subjects and HCM patients with milder hypertrophy (p < 0.001 and p = 0.014, respectively). HCM patients with late gadolinium enhancement (LGE) on CMRI had steeper QTe/RR slopes compared to HCM patients without LGE and control subjects (p = 0.044 and p = 0.001, respectively). LGE was an independent predictor of QTe/RR slope (p = 0.023, B = 0.043).

Conclusion: Dynamics of ventricular repolarization in HCM are affected by hypertrophy and fibrosis. LGE may confer an independent effect on QT dynamics which may increase the arrhythmogenic potential in HCM.

1 | INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden cardiac death in the young and in athletes (Maron, Doerer, Haas, Tierney, & Mueller, 2009; Maron, Haas, Murphy, Ahluwalia, & Rutten-Ramos, 2014). The disease is characterized by ventricular repolarization abnormalities arising from structural changes of cellular hypertrophy, interstitial fibrosis, and myofiber disarray and on the other hand from disturbances in the ion currents and calcium handling on the molecular and cellular level. In combination, these changes constitute the arrhythmic substrate responsible for the risk of malignant ventricular arrhythmias (Coppini et al., 2013; Maron, 2010). The stratification of risk for malignant ventricular arrhythmias in HCM is based on multiple factors, but even with current clinical guidelines gaps remain (Elliott et al., 2014).

The QT interval is prolonged in HCM and modestly correlates with maximal wall thickness (Johnson et al., 2011). The QTe/RR slope has been found steeper in higher risk patients and the QT variance index was slightly elevated in HCM patients with clinically significant arrhythmias (Orosz et al., 2015; Quinteiro et al., 2015). However, data on ventricular repolarization dynamics and their association to the HCM geno- and phenotype are limited.

Fibrosis, as measured by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMRI), is a promising addition to the risk assessment of hypertrophic cardiomyopathy and is a predictor of sudden cardiac death (SCD)(Chan et al., 2014; Weng et al., 2016). The areas of fibrosis in the left ventricle (LV) provide a substrate for ventricular arrhythmias and affect repolarization parameters in monophasic action potential recordings (Sakamoto et al., 2015). The association of LGE to ventricular repolarization dynamics on the surface ECG is unclear. The aim of this study was to explore the dynamics of ventricular repolarization in HCM using ambulatory ECG recordings and analyze the association of hypertrophy and late gadolinium enhancement to the degree of ventricular repolarization disturbances.

2 | METHODS

2.1 | Subjects

Adult Finnish HCM patients carrying either the *MYBPC3*-Q1061X or *TPM*-D175N founder mutation for HCM were recruited prospectively during 2000–2012. HCM was defined in mutation carriers as maximal wall thickness (MWT) ≥13 mm and no other cause for significant hypertrophy. Exclusion criteria were nonsinus rhythm, bundle branch block or implanted pacemaker precluding CMR imaging. Of the screened 52 HCM patients, six were excluded on grounds of nonsinus rhythm (n = 4) or bundle branch block (n = 2). In total, 46 HCM patients were included in the study. Individuals without either of the gene mutations or hypertrophy constituted the control group (n = 35). The Ethics Committees at the Kuopio and Helsinki University Hospitals approved the study protocol. The study conforms to the principles outlined in the Declaration of Helsinki.

2.2 | Baseline data

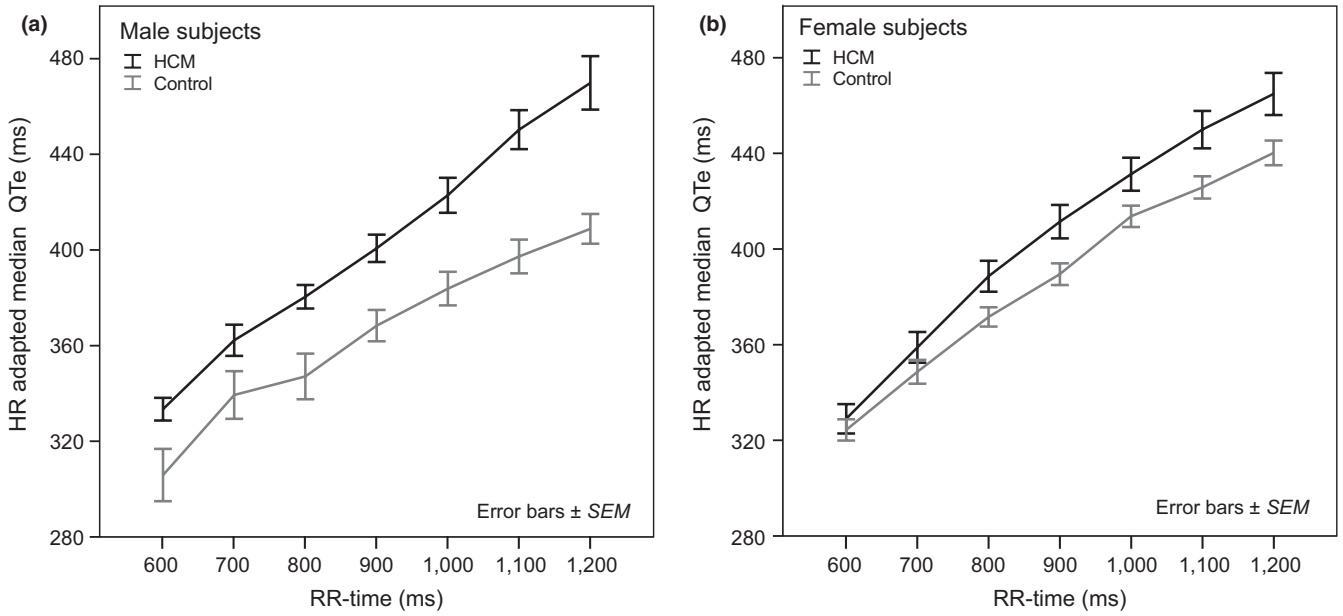
Venous blood samples were collected and measured for creatinine and the plasma concentrations of the N-terminal portion of brain natriuretic peptide (NT-proBNP). Immunoassays utilizing antisera directed to NT-proBNP were used and the sensitivity of the assay was 40 pmol/L (Ala-Kopsala et al., 2005). As previously described, the genetic studies were performed in the Genome Center of Eastern Finland (Jääskeläinen et al., 2002). Normal 12-lead ECG recordings were obtained from subjects and measured for conventional parameters of heart rate, QT-interval duration and corrected QT-interval (using the Bazett formula).

2.3 | Ambulatory ECG analysis

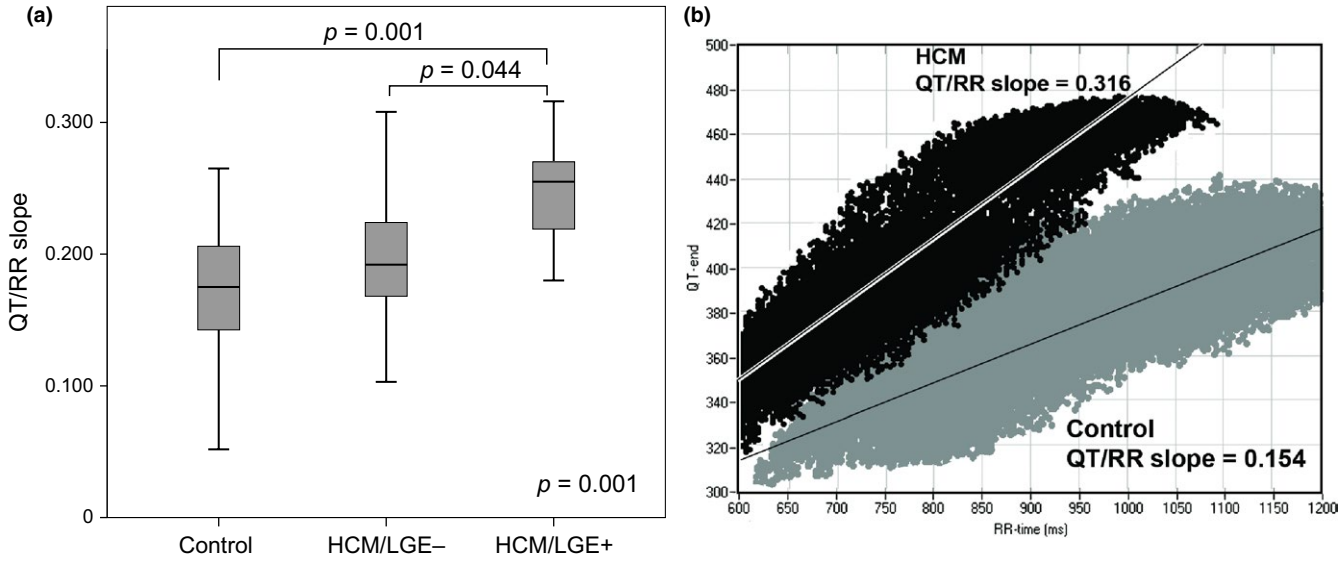
Twenty-four-hour ambulatory ECGs were digitally recorded on Marquette commercial AECG systems and postprocessed with a custom software built in collaboration with Aalto University. Overall quality of the recording was assessed visually using all the available channels (2 or 3 channels). All data were processed and measured from the modified precordial lead V5. All nonsinus beats were excluded. The methodology of data processing and algorithms for determining QRS onset, offset and T-wave peak and T wave end have been previously described (Viitasalo, Oikarinen, Väänänen et al., 2002). T-wave peak was identified as the peak of the parabola fitted to the highest amplitude change after the

heart rates than normal subjects; (b) In HCM, the degree of hypertrophy prolongs the maximal QTe interval; (c) The QTe/RR slope is steeper in HCM than control subjects; (d) HCM patients with LGE show steeper QTe/RR slopes than HCM patients without LGE and LGE is an independent predictor of QTe/RR slope.

We found that the QTe/RR slope was steeper in HCM patients with LGE than those without LGE. In addition, the presence of LGE was the only independent predictor for the steepness of the QTe/RR slope. Previously, a steeper QTe/RR slope has been associated with increased risk of SCD in ischemic patients (Chevalier et al., 2003; Milliez et al., 2005) and overall mortality in heart failure (Cygankiewicz et al., 2008; Pathak et al., 2005; Watanabe et al., 2007). In a study of HCM patients, Quinteiro et al. found the QTe/RR slope steeper in individuals classified as high risk based on conventional risk criteria. Notable in that study was the significant difference in MWT between low and high risk patients (20 mm vs. 25 mm). Although in this study, MWT was associated to prolongation of the QTe, in linear regression the only independent predictor of QTe/RR slope was LGE. In a large cohort of nearly 1,300 HCM patients, an LGE extent of ≥15% of the LV mass was associated with a twofold risk of SCD in HCM patients otherwise classified as low risk (Chan et al., 2014). The fibrosis quantified with LGE may have an additional



& ! ' JHeart rate-adapted QTe intervals for male (a) and female (b) subjects at different heart rates in the two study groups



& ! " J(a) Boxplot of QTe/RR slope in the control group and HCM patients with and without late gadolinium enhancement (LGE). (b) Example of a HCM/LGE+ patient with a QTe/RR slope = 0.316 (black) and a control subject with a QTe/RR slope = 0.154 (gray)

$ " J Repolarization measurements in HCM patients with and without late gadolinium enhancement

Repolarization	HCM/LGE− (n = 29)	HCM/LGE+ (n = 17)	p-Value
QTe (ms)	422 ± 46	410 ± 38	0.367
HR-adapted QTe_{1000} (ms)	424 ± 36	431 ± 32	0.545
Maximum QTe_{1000} (ms)	468 ± 43	470 ± 36	0.886
QTe/RR slope	0.199 ± 0.06	0.242 ± 0.06	0.001
QTp (ms)	324 ± 26	322 ± 38	0.856
HR-adapted QTp_{1000} (ms)	324 ± 26	322 ± 38	0.457
Maximum QTp_{1000} (ms)	368 ± 26	374 ± 38	0.578
TPE (ms)	99 ± 73	85 ± 16	0.478
Median TPE_{1000} (ms)	84 ± 18	94 ± 20	0.168
Maximum TPE_{1000} (ms)	106 ± 24	117 ± 37	0.263

Note. Data presented as mean ± *SD*. The subscript 1,000 denotes measurement at 1,000 ms RR interval duration.
HCM: Hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; QTe: Q wave to T-wave end; TPE: T-wave peak to T-wave end.

role in increasing an HCM patient's risk for ventricular arrhythmias through effects on the propagation of the repolarization current in the myocardium resulting in a steeper QTe/RR slope.

In this study, we found the QTe systematically prolonged in HCM patients, although to a lesser degree than in some previous reports. The reason for this may be, that the patients in this study were relatively asymptomatic and had a mean MWT of 20.6 mm on CMRI compared to, for example, a mean MWT of 24.1 mm in HCM patients with a pathological QTc of ≥480 ms (13% of HCM patients) in a study by Johnson et al. (2011). Prolonged QT interval is associated to increased risk for ventricular arrhythmias (Debonnaire et al., 2015) and independently of hypertrophy predicts ICD therapy in HCM (Gray, Ingles, Medi, & Semsarian, 2013). In healthy individuals, the QT interval is dependent on heart rate in a curvilinear fashion. In this study, the heart rate-adapted QTe in HCM patients prolonged with decreasing heart rates compared to control subjects, resulting in an increasing separation of the QTe curves seen in Figure 1a. This phenomenon is not related to the differences in distribution of RR intervals in the studied ambulatory ECGs. The methodology of using stable heart rates also diminishes the effect of sudden changes in RR intervals to the QTe. The measured maximal and heart rate-adapted median QT peak values followed a very similar pattern to the QTe values and did not offer additional information to the established QTe measurements.

The patterns of ventricular repolarization dynamics were similar between male and female patients with a slight trend for longer QTe values in the female HCM and control subjects. On the other hand, the differences in HR-adapted QTe values between HCM and control subjects were larger in men as compared to women at RR intervals 900–1,200 ms (Figure 3). This was not explained by differences in distribution of maximal wall thickness in male and female HCM patients.

Median TPE was significantly longer in HCM patients with MWT > 20.6 mm compared to the control group in this study. Previously, TPE has been found prolonged in HCM but without analysis of the association to structural changes (Shimizu et al., 2002). The TPE interval has been considered a measure of the global dispersion of ventricular repolarization (Gupta et al., 2008; Opthof et al., 2007) and based on our results is more evident with advanced HCM.

In experimental studies, the prolongation of ventricular repolarization in HCM is the result of pathologies on many levels. The action potential is prolonged as the net repolarizing current is diminished by increased late-type Na and Ca^{2+} currents (I_{NaL} and I_{CaL}) and selective down regulation of the outward rectifying current (I_{Kr}) (Coppini et al., 2013; Crocini et al., 2016; Passini et al., 2016). The repolarization in the myocardium is also delayed due to hypertrophy (Badran et al., 2012) and global repolarization is spatially dispersed due to the asymmetric location of hypertrophy (Sakata et al., 2003). The pathophysiological abnormalities in potassium-currents, especially the reduction in I_{Kr}, resemble those found in type 2 LQTS patients and in agreement we found the prolongation of heart rate-adapted QTe and the prolongation of TPE interval mimicking the findings in type 2 LQTS patients (Viitasalo, Oikarinen, Swan et al., 2002; Viitasalo, Oikarinen, Väänänen et al., 2002).

Approximately, 20%–27% of ICD therapies in HCM patients occur during rest (Maron et al., 2009; O'Mahony et al., 2012). The repolarization alterations in this study increased with lower heart rates and may thus have a role in the ventricular arrhythmias occurring during phases of bradycardia in HCM patients.

4.1 | Limitations of the study

The study was limited in sample size resulting in part from the decision to include only carriers of the two founder mutations. Because of the sample size, the possible effect of sex cannot be definitively ruled out in this study. We did not study the effect of location of hypertrophy on ventricular repolarization parameters, as the absolute number of patients with MWT not localized in the septal segments was relatively small. The assessment of LGE was limited due to different acquisition protocols of CMR imaging and therefore the presence of LGE was assessed only visually with a binary scale because no reliable quantification of LGE extent was possible. The echocardiographic evaluation did not include comprehensive measurements of diastolic function. A number of HCM patients were on beta blocker therapy, which was not discontinued for this study. Beta blocking agents affect the heart rate and may have an influence on the QT to the heart rate relationship. In this study, the mean heart rates were similar between the two study groups and there was no difference in QTe values between HCM patients with and without beta blocker therapy.

5 | CONCLUSIONS

The QTe/RR slope is steeper in HCM patients with LGE independently of hypertrophy. The degree of QTe prolongation is associated to MWT. Overall, the heart rate-adapted QTe is prolonged in HCM patients compared to control subjects. The repolarization dynamics in HCM reflect the underlying changes in the myocardium.

ACKNOWLEDGMENTS

The authors would like to thank Sini Weckström, RN, and Satu Nenonen, RN for data collection.

ORCID

Mikko Jalanko http://orcid.org/0000-0001-5409-3300

REFERENCES

Ala-Kopsala, M., Ruskoaho, H., Leppäluoto, J., Seres, L., Skoumal, R., Toth, M., … Vuolteenaho, O. (2005). Single assay for amino-terminal fragments of cardiac A- and B-type natriuretic peptides. *Clinical Chemistry*, *51*(4), 708–718.

Badran, H. M., Elnoamany, M. F., Soltan, G., Ezat, M., Elsedi, M., Abdelfatah, R. A., & Yacoub, M. (2012). Relationship of mechanical dyssynchrony to QT interval prolongation in hypertrophic cardiomyopathy. *European Heart Journal of Cardiovascular Imaging*, *13*(5), 423–432.

Chan, R. H., Maron, B. J., Olivotto, I., Pencina, M. J., Assenza, G. E., Haas, T., … Maron, M. S. (2014). Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation*, *130*(6), 484–495.

Chevalier, P., Burri, H., Adeleine, P., Kirkorian, G., Lopez, M., Leizorovicz, A., … Touboul, P. (2003). QT dynamicity and sudden death after myocardial infarction: Results of a long-term follow-up study. *Journal of Cardiovascular Electrophysiology*, *14*(3), 227–233.

Coppini, R., Ferrantini, C., Yao, L., Fan, P., Del Lungo, M., Stillitano, F., … Mugelli, A. (2013). Late sodium current inhibition reverses electromechanical dysfunction in human hypertrophic cardiomyopathy. *Circulation*, *127*(5), 575–584.

Crocini, C., Ferrantini, C., Scardigli, M., Coppini, R., Mazzoni, L., Lazzeri, E., … Poggesi, C. (2016). Novel insights on the relationship between T-tubular defects and contractile dysfunction in a mouse model of hypertrophic cardiomyopathy. *Journal of Molecular and Cellular Cardiology*, *91*, 42–51.

Cygankiewicz, I., Zareba, W., Vazquez, R., Almendral, J., Bayes-Genis, A., Fiol, M., … De Luna, A. B. (2008). Prognostic value of QT/RR slope in predicting mortality in patients with congestive heart failure. *Journal of Cardiovascular Electrophysiology*, *19*(10), 1066–1072.

Debonnaire, P., Katsanos, S., Joyce, E., van den Brink, O. V. W., Atsma, D. E., Schalij, M. J., … Marsan, N. A. (2015). QRS fragmentation and QTc duration relate to malignant ventricular tachyarrhythmias and sudden cardiac death in patients with hypertrophic cardiomyopathy. *Journal of Cardiovascular Electrophysiology*, *26*(5), 547–555.

Elliott, P. M., Anastasakis, A., Borger, M. A., Borggrefe, M., Cecchi, F., Charron, P., … Watkins, H. (2014). 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *European Heart Journal*, *35*(39), 2733–2779.

Gray, B., Ingles, J., Medi, C., & Semsarian, C. (2013). Prolongation of the QTc interval predicts appropriate implantable cardioverter-defibrillator therapies in hypertrophic cardiomyopathy. *JACC: Heart Failure*, *1*(2), 149–155.

Gupta, P., Patel, C., Patel, H., Narayanaswamy, S., Malhotra, B., Green, J. T., … Yan, G.-X. (2008). T(p-e)/QT ratio as an index of arrhythmogenesis. *Journal of Electrocardiology*, *41*(6), 567–574.

Jääskeläinen, P., Kuusisto, J., Miettinen, R., Kärkkäinen, P., Kärkkäinen, S., Heikkinen, S., … Laakso, M. (2002). Mutations in the cardiac myosin-binding protein C gene are the predominant cause of familial hypertrophic cardiomyopathy in eastern Finland. *Journal of Molecular Medicine*, *80*(7), 412–422.

Johnson, J. N., Grifoni, C., Bos, J. M., Saber-Ayad, M., Ommen, S. R., Nistri, S., … Ackerman, M. J. (2011). Prevalence and clinical correlates of QT prolongation in patients with hypertrophic cardiomyopathy. *European Heart Journal*, *32*(9), 1114–1120.

Maron, B. J. (2010). Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. *Circulation*, *121*(3), 445–456.

Maron, B. J., Doerer, J. J., Haas, T. S., Tierney, D. M., & Mueller, F. O. (2009). Sudden deaths in young competitive athletes: Analysis of 1866 deaths in the United States, 1980-2006. *Circulation*, *119*(8), 1085–1092.

Maron, B. J., Haas, T. S., Murphy, C. J., Ahluwalia, A., & Rutten-Ramos, S. (2014). Incidence and causes of sudden death in U.S. college athletes. *Journal of the American College of Cardiology*, *63*(16), 1636–1643.

Maron, B. J., Semsarian, C., Shen, W.-K., Link, M. S., Epstein, A. E., Estes, N. A. M., … Spirito, P. (2009). Circadian patterns in the occurrence of malignant ventricular tachyarrhythmias triggering defibrillator interventions in patients with hypertrophic cardiomyopathy. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, *6*(5), 599–602.

Milliez, P., Leenhardt, A., Maisonblanche, P., Vicaut, E., Badilini, F., Siliste, C., … Coumel, P. (2005). Usefulness of ventricular repolarization dynamicity in predicting arrhythmic deaths in patients with ischemic cardiomyopathy (from the European Myocardial Infarct Amiodarone Trial). *American Journal of Cardiology*, *95*(7), 821–826.

O'Mahony, C., Lambiase, P. D., Rahman, S. M., Cardona, M., Calcagnino, M., Quarta, G., … Elliott, P. (2012). The relation of ventricular arrhythmia electrophysiological characteristics to cardiac phenotype and circadian patterns in hypertrophic cardiomyopathy. *EP Europace*, *14*(5), 724–733.

Opthof, T., Coronel, R., Wilms-Schopman, F. J. G., Plotnikov, A. N., Shlapakova, I. N., Danilo, P., … Janse, M. J. (2007). Dispersion of repolarization in canine ventricle and the electrocardiographic T wave: Tp-e interval does not reflect transmural dispersion. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, *4*(3), 341–348.

Orosz, A., Baczkó, I., Nagy, V., Gavallér, H., Csanády, M., Forster, T., … Sepp, R. (2015). Short-term beat-to-beat variability of the QT interval is increased and correlates with parameters of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy. *Canadian Journal of Physiology and Pharmacology*, *93*(9), 765–772.

Passini, E., Mincholé, A., Coppini, R., Cerbai, E., Rodriguez, B., Severi, S., & Bueno-Orovio, A. (2016). Mechanisms of pro-arrhythmic abnormalities in ventricular repolarisation and anti-arrhythmic therapies in human hypertrophic cardiomyopathy. *Journal of Molecular and Cellular Cardiology*, *96*, 72–81.

Pathak, A., Curnier, D., Fourcade, J., Roncalli, J., Stein, P. K., Hermant, P., … Galinier, M. (2005). QT dynamicity: A prognostic factor for sudden cardiac death in chronic heart failure. *European Journal of Heart Failure*., *7*(2), 269–275.

Quinteiro, R. A., Biagetti, M. O., Fernandez, A., Borzone, F. R., Gargano, A., & Casabe, H. J. (2015). Can QT/RR relationship differentiate between low- and high-risk patients with hypertrophic cardiomyopathy? *Annals of Noninvasive Electrocardiology*, *20*(4), 386–393.

Sakamoto, N., Kawamura, Y., Sato, N., Nimura, A., Matsuki, M., Yamauchi, A., … Hasebe, N. (2015). Late gadolinium enhancement on cardiac magnetic resonance represents the depolarizing and repolarizing electrically damaged foci causing malignant ventricular arrhythmia in hypertrophic cardiomyopathy. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, *12*(6), 1276–1284.

Sakata, K., Shimizu, M., Ino, H., Yamaguchi, M., Terai, H., Hayashi, K., … Mabuchi, H. (2003). QT dispersion and left ventricular morphology in patients with hypertrophic cardiomyopathy. *Heart*, *89*(8), 882–886.

Shimizu, M., Ino, H., Okeie, K., Yamaguchi, M., Nagata, M., Hayashi, K., … Mabuchi, H. (2002). T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. *Clinical Cardiology*, *25*(7), 335–339.

Viitasalo, M., Oikarinen, L., Swan, H., Väänänen, H., Glatter, K., Laitinen, P. J., … Scheinman, M. M. (2002). Ambulatory electrocardiographic evidence of transmural dispersion of repolarization in patients with long-QT syndrome type 1 and 2. *Circulation*, *106*(19), 2473–2478.

Viitasalo, M., Oikarinen, L., Väänänen, H., Swan, H., Piippo, K., Kontula, K., … Scheinman, M. M. (2002). Differentiation between LQT1 and LQT2 patients and unaffected subjects using 24-hour electrocardiographic recordings. *American Journal of Cardiology*, *89*(6), 679–685.

Watanabe, E., Arakawa, T., Uchiyama, T., Tong, M., Yasui, K., Takeuchi, H., … Hishida, H. (2007). Prognostic significance of circadian variability of RR and QT intervals and QT dynamicity in patients with chronic heart failure. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, *4*(8), 999–1005.

Weng, Z., Yao, J., Chan, R. H., He, J., Yang, X., Zhou, Y., & He, Y. (2016). Prognostic Value of LGE-CMR in HCM: A Meta-Analysis. *JACC: Cardiovascular Imaging*, *9*(12), 1392–1402.

How to cite this article: Jalanko M, Väänänen H, Tarkiainen M, et al. Fibrosis and wall thickness affect ventricular repolarization dynamics in hypertrophic cardiomyopathy. *Ann Noninvasive Electrocardiol*. 2018;23:e12582. https://doi.org/10.1111/anec.12582